Reviewer’s report

Title: A multi-center randomized, controlled, open-label trial evaluating the effects of eosinophil-guided corticosteroid-sparing therapy in hospitalised patients with COPD exacerbations - The CORTICOsteroid reduction in COPD (CORTICO-COP) study protocol

Version: 0 Date: 13 Mar 2017

Reviewer: Mark Dransfield

Reviewer's report:

Title: A randomized, GCP-controlled, multi-center trial evaluating the effects of eosinophil-guided corticosteroid-sparing therapy in hospitalised patients with COPD exacerbations - The Corticosteroid reduction in COPD (CORTICO-COP) Study protocol

Summary: This submission is an overview of the study protocol for the CORTICO-COP Study by Sivalapan et al that is currently recruiting participants. The investigators note that high-dose systemic corticosteroids are frequently prescribed in acute exacerbations of COPD with no proven mortality benefit but with significant potential for side effects. Given the growing evidence supporting eosinophil levels as a means to target steroids in COPD, the study aims to test an intervention to reduce corticosteroid prescribing during acute exacerbations without negatively impacting outcomes. The primary aim of the proposed prospective randomized controlled trial is to determine if a serum eosinophil-guided strategy is non-inferior to usual care. The primary outcome is the length of hospitalization OR number of days alive and out of hospital within 14 days of an acute exacerbation though the authors should more clearly state the primary endpoint and be consistent throughout. The investigators also seek to assess treatment failure, 30-day mortality rate, change in FEV1, change in COPD Assessment Test score and dyspnea, cumulative steroid dose, time to next acute exacerbation, and the number of systemic adverse effects of corticosteroids within 3 months. The investigators propose to assess numerous systemic adverse effects, namely hyperglycemia, osteopenia, dyspepsia, diabetes mellitus, increased body mass index, and other infections requiring antibiotics. The trial seeks to enroll 320 participants during an acute exacerbation of COPD and blindly randomize participants in a 1:1 fashion to "eosinophil-guided corticosteroid-sparing therapy" versus "standard care". Specifically, the investigators propose that participants in the intervention group receive methylprednisolone 80g intravenous on day 1 followed by a maximum of 4 days of 37.5mg of oral prednisolone only administered on days when the serum eosinophil count is ≥300 cells/µL. The comparison group of standard care will receive methylprednisolone 80g intravenous on day 1 followed by 37.5mg of oral prednisolone for 4 days. The method chosen for statistical analysis will be non-inferiority on the primary endpoint. The investigators have selected broad inclusion on criteria and limited exclusion criteria.
Major Comments:

- Please clarify the primary endpoint and be consistent throughout. Specifically, what is the difference between a "relevant increase in length of hospitalization for AECOPD patients receiving eosinophil guided prednisolone-sparing therapy compared to SC" vs "Days alive and out of hospital within 14 days after recruitment". The authors state power was based on the first, so that needs to be clear and consistent. The second is not clear.

- The investigators should move the Anthonisen criteria for an acute exacerbation of COPD from the section on measurements to the inclusion criteria and detail the plan to identify these participants.

- Would add fractures and explain "infections that require antibiotics" as secondary endpoints.

- Diabetes mellitus is an odd secondary endpoint, unless it is incident diabetes. This should be clarified. Perhaps, just hyperglycemia should be the secondary endpoint.

- Please explain what is meant by "GCP" in the title - perhaps best not to use abbreviation.

Minor Comments:

- Page 10, Line 46: "has" to have. This sentence is confusing and should be clarified.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal